Myocardial Metabolic Studies in Prolapsing Mitral Leaflet Syndrome

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SUMMARY

Patients with prolapsing mitral leaflet syndrome (PML) frequently have chest pain of undetermined etiology. Twenty-three patients with PML underwent cardiac hemodynamic, angiographic, and metabolic studies. The latter were performed during control spontaneous heart rate and tachycardia by right atrial pacing. Myocardial supply-demand ratio (DPTI:SPTI) was estimated from the planimetric integration of the diastolic area (diastolic pressure time index = DPTI) and systolic area (systolic pressure time index = SPTI) of the central aortic pressure. Chest pain during pacing occurred in five patients. In two patients, it was associated with ST depression typical of ischemia on the electrocardiogram. Myocardial lactate abnormalities (lactate production or less than 10% extraction) occurred in seven patients during pacing tachycardia and was present in two patients during control state. DPTI:SPTI ratio during control state was 1.22 (± 0.07 SE) and decreased to 0.85 (± 0.05 SE) during pacing tachycardia. It is concluded that the myocardial lactate abnormalities in PML, which were present in approximately 30% of the patients in the present series, are most likely due to myocardial hypoxia. Whether or not the hypoxia is secondary to "small vessel disease" is not elucidated by this study.

Patients with prolapsing mitral leaflet syndrome (PML) frequently have chest pain which may even have anginal characteristics. Coronary cineangiograms, however, generally do not reveal any obstructive lesion. So far the role of myocardial ischemia as the cause of chest pain in PML has not been established. In this regard, myocardial metabolic studies may help to elucidate the importance of myocardial ischemia. It is the purpose of this communication to report our findings in a group of patients with PML who underwent myocardial metabolic studies during a resting state and also during pacing tachycardia. The results of these studies indicate that approximately 30% of patients with PML have myocardial lactate abnormalities suggestive of myocardial hypoxia.

Material and Method

Twenty-three patients with PML formed the material of this study. They were among 609 patients who had cardiac hemodynamic and angiographic studies during a two-year period. There were five males and 18 females ranging in age from 31 to 61 years (mean age = 46 years). Seventeen patients had exertional chest pain, five had chest pain at rest, and one patient had episodes of ventricular tachycardia. All the patients had complete history and physical examination, serial electrocardiogram, and in many cases serum enzyme determinations because of persistent chest pain and/or arrhythmias. Because of the presence of systolic murmur (13 patients) and click (five patients), the diagnosis of PML was suspected in most cases prior to cardiac catheterization. Although some of the patients had been treated with propranolol, this medication was discontinued at least 48 hours prior to cardiac catheterization.

Right heart catheterization in postabsorptive state was performed in 16 patients using the standard technique and after premedication with diphenhydramine hydrochloride and sodium pentobarbital, 25 mg intramuscularly each. Left ventriculograms in the 30° right anterior oblique view were obtained after injecting 40–50 ml methylglucamine diatrizoate (Renografin 76) under 100–150 psi pressure through a No. 7F NIH catheter. The diagnosis of PML was based on the left ventriculographic finding of prolapse of the posterior or anterior mitral leaflets during systole since mitral regurgitation, systolic click, or systolic murmur may not be consistently present in this syndrome. Special attention was paid to the mitral valve and leaflets, foramin (which may simulate a slight degree of prolapse), presence of mitral regurgitation, and the geometry and contraction pattern of the left ventricle.

Selective coronary cineangiograms in multiple views were obtained using Sones technique.1 No patient with coronary artery disease and prolapse of the mitral leaflets was included in this series since the prolapse could then be secondary to papillary muscle dysfunction on the basis of coronary artery disease.

Myocardial metabolic studies were performed during control state and right atrial pacing tachycardia. The latter was accomplished by positioning the tip of a No. 6F bipolar electrode catheter in the right atrium and stimulating by a

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Cordis generator, model Chronacor III at threshold MA and fixed mode. The paced rate was gradually increased until the patient developed Wenckebach block, chest pain, or a maximal heart rate of 160 beats/min was reached. Arterial and coronary sinus blood lactate was determined in duplicate using the enzymatic method. Blood oxygen content was measured by spectrophotometry.

To determine the importance of subendocardial ischemia, the ratio between myocardial oxygen supply and demand was estimated as follows\(^2\)\(^-\)\(^4\) (fig. 1): Diastolic pressure-time index (DPTI) as an estimate of myocardial blood supply was measured by planimetric integration of the area under the diastolic phase of the central aortic pressure minus pulmonary wedge pressure (in 16) or left ventricular end-diastolic pressure (LVEDP) (in seven). Myocardial oxygen demand was estimated from the systolic pressure-time index (SPTI) by planimetric integration of the area under the systolic phase of the aortic pressure. The ratio DPTI:SPTI was then used as an estimate of the subendocardial oxygenation. The average of ten cardiac cycles was used in each case. All the pressures were recorded on Electronics-for-Medicine photographic recorder, model DR-8, at a paper speed of 25 mm/sec and 100 mm/sec. Myocardial metabolic studies were considered abnormal if there was lactate production or less than 10% extraction. ST-segment abnormalities were considered to be present when 1 mm depression or more occurred immediately after cessation of the pacing.

**Results**

**Cardiac Hemodynamic Findings During Control State (table 1)**

The cardiac index was 3.51 L/min/m\(^2\) (± 0.25 standard error [SE]). The left ventricular systolic pressure was 122.7 mm Hg (± 3.1 SE) and the LVEDP was 8.8 mm Hg (± 1.1 SE). There were only three patients with abnormally elevated LVEDP (17, 24, and 14 mm Hg). Mean pulmonary wedge and pulmonary arterial pressures were 5.3 mm Hg (± 0.7 SE) and 10.5 mm Hg (± 0.8 SE) respectively. Right ventricular end-diastolic pressure (RVEDP) was 4.4 mm Hg (± 0.7 SE) with six patients having abnormally elevated RVEDP (range

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**Figure 1**

Subendocardial supply-demand ratio (DPTI:SPTI) during control state (A) and pacing tachycardia (B) is estimated from the central aortic pressure tracing. SPTI is estimated from the planimetric integration of the systolic portion of the aortic tracing (stippled area). DPTI is estimated from the planimetric integration of the area under the diastolic portion of the aortic pressure (clear area) minus the pulmonary wedge pressure (PW) or left ventricular end-diastolic pressure.
PROLAPSING MITRAL LEAFLET

Table 1
Cardiac Hemodynamic Data During Control Resting State

<table>
<thead>
<tr>
<th></th>
<th>CI (L/min/m²)</th>
<th>SI (ml/beat/m²)</th>
<th>EF</th>
<th>PW</th>
<th>FA</th>
<th>RV</th>
<th>RA</th>
<th>Ao</th>
<th>LV</th>
<th>Vascular resistances (dynes sec^-1 cm^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.51</td>
<td>46.2</td>
<td>0.71</td>
<td>17.5</td>
<td>6.4</td>
<td>(10.5)</td>
<td>22.0</td>
<td>4.4</td>
<td>0.7</td>
<td>8.9</td>
</tr>
<tr>
<td>±± SE</td>
<td>0.25</td>
<td>2.2</td>
<td>0.01</td>
<td>0.8</td>
<td>0.5</td>
<td>0.8</td>
<td>1.8</td>
<td>0.7</td>
<td>0.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Abbreviations: Ao = aorta; CI = cardiac index; D = diastolic pressure; EF = ejection fraction; PW = pulmonary wedge; PAR = pulmonary arteriolar resistance; PA = pulmonary artery; RA = right atrium; RV = right ventricle; S = systolic pressure; SI = stroke index; TPR = total pulmonary vascular resistance; TSR = total systemic resistance.

6–10 mm Hg). Right atrial mean pressure was normal in all. Aortic systolic, diastolic, and mean pressures were 121 mm Hg (± 4.0 SE), 71.1 mm Hg (± 2.2 SE), and 90.8 mm Hg (± 2.7 SE) respectively. Total pulmonary arterial and pulmonary arteriolar resistances were 150.2 dynes sec^-1 cm^-1 (± 10.4 SE), and 70.2 dynes sec^-1 cm^-1 (± 3.9 SE) respectively.

Left Ventriculographic and Coronary Arteriographic Findings

All the patients had prolapse of the posterior leaflet of the mitral valve (fig. 2). Two patients had associated prolapse of the anterior leaflet (4 and 18). In addition, abnormalities of the left ventricular geometry and contraction (inferior and anterior bulges, asynchrony of contraction, cavity obliteration) were present in all the cases. Mitral regurgitation was detected in three patients. No patient had occlusive coronary artery disease (defined as more than 20% constriction in any vessel) but corkscrew appearance of the vessels was frequently noted. Ejection fraction was 0.71 (± 0.01 SE). Cardiomegaly was not present in any case.

Electrocardiographic Findings

Stable or unstable ST-T abnormalities were present in all the patients. These abnormalities were either diffuse or localized to anterior or inferior wall. In addition, ventricular arrhythmias or history of palpitation were present in most of the patients.

Immediately following the pacing tachycardia, 1 mm (or more) ST depression occurred in four patients (fig. 3 and table 2). This was associated with chest pain in two patients. Three additional patients developed chest pain not accompanied by ST depression.

Myocardial Metabolic Findings (figs. 4 and 5, table 2)

Myocardial lactate abnormalities (less than 10% extraction or lactate production) during control state occurred in two patients (6% extraction in case 19 and lactate production in case 20). During pacing tachycardia, seven patients developed lactate abnormalities (2, 5, 8, 11, 12, 19, 20), six of them lactate production. Myocardial oxygen extraction ratio (arterial-coronary sinus oxygen content × 100) during control state was 60.3% (± 3.2 SE) and during pacing tachycardia was 57.9% (± 1.6 SE). Myocardial lactate abnormalities were not related to the degree of leaflet prolapse, prolapse of the anterior or posterior leaflet (or both), magnitude of the left ventricular contractile abnormalities or ejection fraction. Of seven patients with lactate abnormality, six had exertional chest pain.

Figure 2

Selected frames of the left ventriculogram in right anterior oblique view during systole (a) and diastole (b). The prolapse of the posterior leaflet of the mitral valve is indicated by the arrows. A slight degree of mitral regurgitation is also present.
### Table 2

**Myocardial Metabolic Data During Control State and Pacing Tachycardia**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Control</th>
<th>Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lactate (mEq/L)</td>
<td>Oxygen (vol %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ao-Cₐ, % extr</td>
<td>Ao-Cᵦ, % extr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPTI</td>
<td>SPTI</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>68</td>
<td>0.52</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>79</td>
<td>0.27</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>107</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>55</td>
<td>0.13</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>90</td>
<td>0.13</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>72</td>
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<td>7</td>
<td>59</td>
<td>86</td>
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<tr>
<td>8</td>
<td>46</td>
<td>58</td>
<td>0.18</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
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<td>0.54</td>
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<tr>
<td>10</td>
<td>50</td>
<td>60</td>
<td>0.53</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>74</td>
<td>0.19</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>53</td>
<td>0.49</td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>87</td>
<td>0.50</td>
</tr>
<tr>
<td>14</td>
<td>57</td>
<td>59</td>
<td>0.12</td>
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<td>39</td>
<td>79</td>
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<tr>
<td>16</td>
<td>34</td>
<td>67</td>
<td>0.17</td>
</tr>
<tr>
<td>17</td>
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<td>60</td>
<td>0.31</td>
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<tr>
<td>18</td>
<td>53</td>
<td>78</td>
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<td>19</td>
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<td>74</td>
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<td>43</td>
<td>78</td>
<td>-0.04</td>
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<td>21</td>
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<tr>
<td>23</td>
<td>40</td>
<td>64</td>
<td>0.18</td>
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</table>

Mean ± se

<table>
<thead>
<tr>
<th></th>
<th>Lactate (mEq/L)</th>
<th>Oxygen (vol %)</th>
<th>DPTI</th>
<th>SPTI</th>
<th>HR</th>
<th>Lactate (mEq/L)</th>
<th>Oxygen (vol %)</th>
<th>DPTI</th>
<th>SPTI</th>
<th>ST</th>
<th>Chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>75.3 ± 3.3</td>
<td>10.5 60.3</td>
<td>1.22 41.7</td>
<td>*</td>
<td>* 10.1 57.9</td>
<td>0.85</td>
<td>0.36</td>
<td>1.6 0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Mean myocardial lactate values are not computed because of negative arteriovenous lactate difference in one patient during control state and in six patients during pacing.

Abbreviations: Ao = aorta; Cᵦ = coronary sinus; DPTI = diastolic pressure time index; HR = heart rate; SPTI = systolic pressure time index; % extr = percent extraction (extraction ratio); ST = ST segment depression.

**Myocardial Oxygen Demand: Supply Ratio (DPTI:SPTI)**

The mean ratio in control state was 1.22 (± 0.07 se) and decreased to 0.85 (± 0.05 se) during pacing tachycardia. There was no correlation between this ratio and electrocardiographic abnormalities, chest pain, or myocardial lactate abnormalities.

**Discussion**

This study demonstrates that approximately 30% (seven out of 23) of patients with PML have myocardial lactate abnormalities. Since these metabolic abnormalities are usually associated with myocardial hypoxia, it may then be suggested that perhaps some

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Figure 3

Lead II ECG during control state (A) and immediately after cessation of pacing tachycardia (B). Note the marked downsloping ST depression in the lower tracing.

of the clinical features of these patients, i.e., chest pain, electrocardiographic abnormalities, ventricular arrhythmias and abnormalities of myocardial geometry and contraction are also caused by myocardial ischemia.

Gooch et al.,

emphasizing the frequency of these ventriculographic abnormalities, suggested that PML may be a form of functional cardiomyopathy. Pasternac et al.

have also reported the presence of myocardial lactate abnormalities in patients with PML; however these authors concluded that the lactate abnormalities were probably not the result of ischemia. Their conclusion was based on the finding that the lactate abnormalities were more marked during control state as compared to tachycardia. In our study, on the contrary, myocardial lactate abnormalities occurred in seven patients during pacing tachycardia and only in two patients these abnormalities were present at rest. In one of these two (19), there was 6% lactate extraction during control state which progressed to lactate production during pacing tachycardia.

Hence in our study, myocardial lactate abnormalities are suggestive of myocardial ischemia. On the other hand, our failure to find a correlation between myocardial lactate abnormalities and occurrence of chest pain argues against the conclusion that myocardial ischemia is the underlying mechanism. However this discrepancy between metabolic abnormalities and chest pain also exists in patients who clearly have myocardial ischemia on the basis of angiographically-proven coronary artery disease. In addition, patients with "angina and normal coronary arteriograms" reflect a similar lack of correlation. Myocardial lactate

Figure 4

Myocardial arteriovenous lactate difference during control state and pacing tachycardia.

Circulation, Volume 52, December 1975

Figure 5

Myocardial oxygen extraction ratio during control state and pacing tachycardia. Vertical bars represent mean ± SE.
abnormalities during control resting state have also been reported in patients with coronary artery disease.\textsuperscript{11, 12}

Thus the lactate abnormalities in the present series are most likely suggestive of myocardial hypoxia. Whether or not the hypoxia is due to "small vessel disease\textsuperscript{13-16} or to abnormalities of cellular metabolism inherent in the cardiomyopathy is not elucidated by this study. In general, lactate abnormalities were more frequent in patients with exertional chest pain, although five patients with chest pain at rest and the patient with ventricular tachycardia had normal lactate metabolism.

Our current thinking is as follows: PML most likely reflects two different underlying mechanisms. In one, there is cardiomyopathy and the prolapse of the mitral valve is secondary to abnormalities of myocardial contraction. In the other category, the pathology is "primarily" in the mitral valve or chordae tendineae and thus the electrocardiographic abnormalities and arrhythmias may be mechanically induced by the impact of the abnormally large leaflets and long chordae on the ventricular wall.

In the present study, DPTI:SPTI ratio was not suggestive of subendocardial ischemia. Our lowest ratio (0.55 in case 20 during pacing tachycardia) was higher than the ratio Barnard et al.\textsuperscript{8} recorded when ischemic electrocardiographic abnormalities appeared. This discrepancy could be explained by the presence of small vessel disease. The DPTI:SPTI ratio is based on the assumption that there is no coronary artery disease and hence the diastolic pressure in the coronary arteries is the same as in the aorta. If our patients with PML had "small vessel disease," then DPTI cannot be used as an estimate of myocardial blood supply.

In conclusion, the present study indicates the approximately 30\% of patients with PML have myocardial lactate abnormalities which are usually seen in myocardial hypoxia. Because of chest pain, electrocardiographic abnormalities, and myocardial metabolic abnormalities in the presence of normal coronary arteriograms, myocardial hypoxia, possibly due to "small vessel disease" or cellular abnormalities, is strongly suggested.

References

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